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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF DIAZAPHENANTHRENO ISOINDOLES (PYRIDO BENZOXAZINES)

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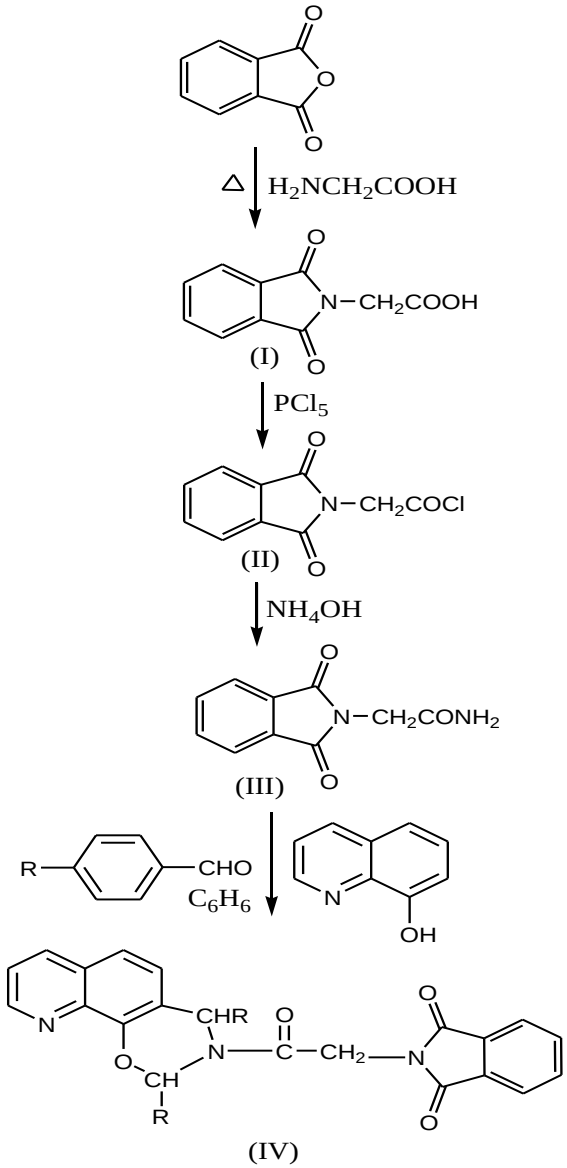
***Abstract*—Four new diazaphenanthreno isoindoles (pyridobenzoxazines) were synthesized taking isobenzofuran-1,3-dione (phthalic anhydride) as the starting material. Thus, heating of benzofuran-1,3-dione and glycine at 185-190ºC in equimolar amounts resulted in (1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetic acid (I) which on reaction with PCl_5 afforded (1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetylchloride (II).The reaction of (II) with NH4OH yielded (III) which on reaction with 8-hydroxy quinoline and various aromatic aldehydes in benzene solution furnished the desired compounds (IV) in moderate yields. The target molecules (IV) were evaluated against the six strains of fungi. (SCHEME)**

Index Terms— PYRIDO BENZOXAZINES, ANTIFUNGAL ACTIVITY, DIAZAPHENANTHRENO ISOINDOLES, Quinoline Substructure.

I. INTRODUCTION

Benzoxazine compounds have been demonstrated to be useful agents in various health areas including their potentials as antifungal agents[1-3]. In addition the chemical reactivity of pharmacologically active benzoxazinoid derivatives towards various types of nucleophiles has been reviewed in relation to their biological activity[4]. Since target molecules contain a quinoline substructure, it is expected that such compounds might render improved therapeutic results as quinolines have been in clinical practice since a long time as antimicrobial and antiparasitic agents. However, the antimicrobial activity may depend upon the isoindole and oxazine moieties which are present in this molecular architecture.



SCHEME

II. EXPERIMENTAL

Melting points were determined in the open glass capillary tubes in the Toshniwal electric apparatus (Japan) and the values reported are uncorrected. The infrared (i.r.) spectra were recorded in the region 4000-400 cm^{-1} range using KBR discs on FTIR 8201 VC Parkin Elmer spectrophotometer model 337 (USA) at CDRI, Lucknow. The ^{1}HNMR and ^{13}C NMR spectra were recorded on Bruker DRX 200MHz spectrometer at CDRI, Lucknow using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was used as an internal standard and the values of chemical shifts have been expressed in δ(ppm). The fast atom bombardment (FAB) mass spectra were recorded on JEOL 5X 102/DA-600 mass spectrometer in which p-nitrobenzyl alcohol was used as a matrix. The biological activity data were collected from, CDRI, Lucknow.

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) acetic acid (I)
A white crystalline mass, m.p. 191^{0}C [192^{0}C][5]

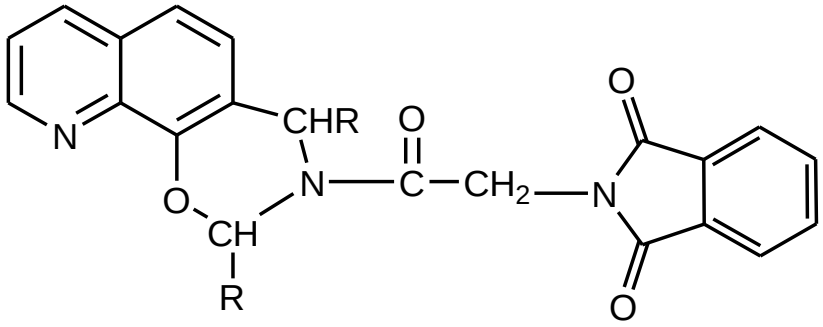
(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) acetylchloride(II)
White solid, was used for the further reaction without recrystallization.

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) acetamide(III)
White crystalline solid, m.p. 109^{0}C [210^{0}C][6].

2-[2-(1,3-Diaryl-1H-4-oxa-2,5-diazaphenanthren-2-yl)-2-oxo-isoindole-1,3-diones] (IV)

A mixture consisting (1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetamide (III) (0.01mole), 8-hydroxyquinoline(oxime) (0.01mole) and an aromatic aldehyde (0.02 mole) in dry benzene (100ml) was heated under reflux for six hours under anhydrous reaction conditions. Subsequently, solvent benzene was distilled off under diminished pressure. The pasty solid separated out, was triturated with petroleum ether (b.p. 60-80^{0}C). the solidified material thus obtained was washed with cold water and dried over vacuo. The compound thus isolated, were recrystallized from diluted ethanol and their characterization data recorded in Table-I.

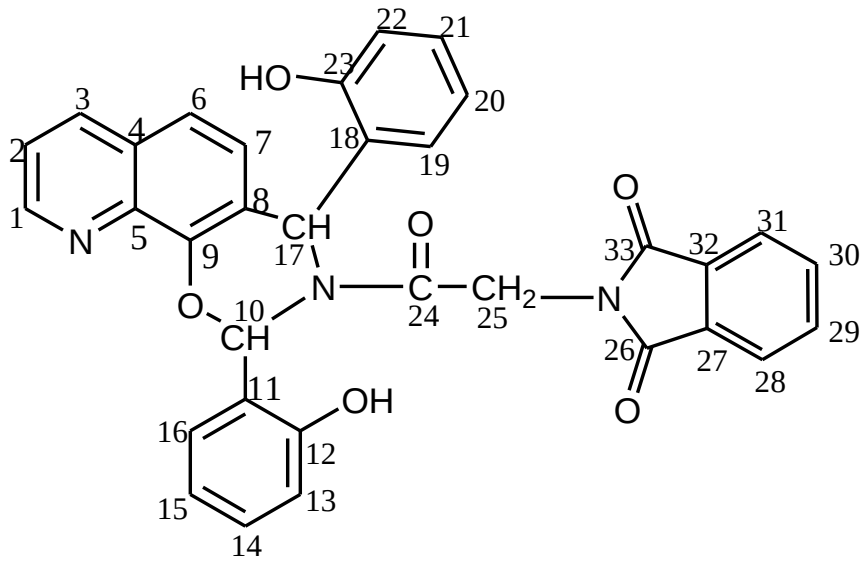
TABLE-I



Characterization data of 2-[2-(1,3-diaryl-4-oxa-2,5-diazaphenanthren-2-yl)-2-oxo-methyl]-isoindole-1,3-diones (IV)

Compd No	R	m.p. (^{0}C)	yield	colour	Molecular formula	Molecular weight	Analysis Nitrogen %	
							Calcd.	found
1	Phenyl	130	70	green	$C_{33}H_{23}N_3O_4$	525	8.00	8.12
2	2-hydroxy-phenyl	105	70	Light green	$C_{33}H_{23}N_3O_6$	557	7.54	8.00
3	4-hydroxy phenyl	125	60	Light green	$C_{33}H_{23}N_3O_6$	557	7.54	7.75
4	4-methoxy phenyl	110	50	Dark green	$C_{35}H_{27}N_3O_6$	585	7.17	7.50

Spectral data of 2-[2'-(1,3-di-o- hydroxy phenyl-4 -oxa-2,5-diazaphenanthren-2-yl)-2-oxo-methyl] isoindole-1,3-dione (Compd. No.2 of the Table-I)



IR (KBr, ν_{max} cm^{-1}) : 1095 ($\geq C-O-C$), 1718 (imido C = O), 3663(ArOH)

^{1}HNMR ($CDCl_3$, in δ ppm) :7.08-7.94 (m,19H, Ar<u>H</u>), 4.32(s, 1H, N-C<u>H</u>-O), 2.50(s, 1H, C-C<u>H</u>-N), 3.44 ($-\overset{\overset{O}{\|}}{C}-C\underline{H}_2-N$), 9.55 (trs, 2<u>H</u>, ArO<u>H</u>)

^{13}CNMR($CDCl_3$) : 45.1(C-25), 50.2(C-10), 111.5, 112.2, 114.4, 115.2, 117.3, 121.4, 122.3, 125.7,

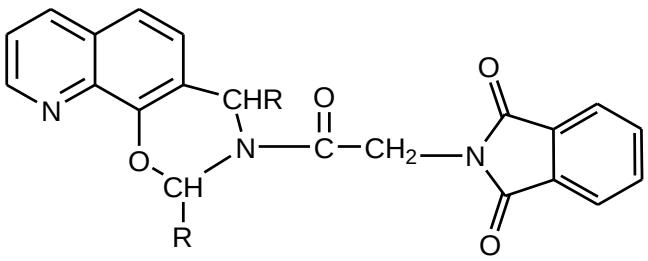
128.2, 131.3, 134.4, 135.6, 137.2, 139.8, 141.4(C-2 to C-5), (C-6 to C-9), (C-11 to C-16), (C-18 to C-23), 166.4(C-1), 169.7(C-24), 171.5(C-26, C-33)

Mass spectrum (FAB) : M+ was not observed, base peak appeared at 146, other important peaks appeared at m/z 89, 107, 146, 160, 188, 206, 234, 344 and 454.

III. ANTIFUNGAL ACTIVITY

All the four compounds of the final category were evaluated for their antifungal activity against six fungal strains viz; *Candida albicans* (Ca), *Cryptococcus neoformans* (Cn), *Sporothrix schenkii* (Ss), *Trichophyton mentagrophytes* (Tm), *Aspergillus fumigatus* (Af) and *Candida parapsilosis* (Cp) invitro involving the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The antifungal activity data are incorporated in Table-II.

TABLE-II



Antifungal activity data of 2-[2'-(1,3-diaryl- 4 -oxa-2,5-diazaphenanthren-2-yl)-2-oxo-methyl] isoindole-1,3-diones

Compd. No.	R	Minimum inhibitory concentration (MIC) in µg/ml					
		Ca	**Cn**	**Ss**	**Tm**	**Af**	**Cp**
1	phenyl	25	50	25	12.5	25	50
2	2-hydroxyphenyl	12.5	12.5	6.25	6.25	50	>50
3	4-hydroxyphenyl	6.25	6.25	1.56	1.56	12.5	25
4	4-methoxyphenyl	50	50	>50	25	50	25

IV. RESULT AND DISCUSSION

The antifungal activity data incorporated in Table-II indicate that all the four compounds have potentials to provoke fungal inhibitory properties. Out of the four compounds evaluated the compound no. 4 was more reactive against four fungal strains viz; against Ca, Cn, Sc, Tm, Af and Cp with lower MIC values of 6.25, 6.25, 1.56, 1.56, 12.5, 25 respectively. It is interesting to observe here that the compound no.2 having 2-hydroxy substituent was less antifungal active than the compound no.3 containing a 4-hydroxy substituent. It is inferred here that a 4-hydroxy phenyl substituted compound finds a better fit at the receptor site. However, more biological activity data are required to predict the antifungal potentials of such compounds.

V. ACKNOWLEDGEMENT

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VI. REFERENCES

[1] Kobayashi,K., Okamura,Y. and Konish, H., Synthesis, 1494-1498(2009).

[2] Sicker,D., Hartenstein,H. and Kluge,K., J.Med.Chem., 36, 461-475 (1979).

[3] Khan, R.H. and Rastogi, R., Ind.J.Chem., 32, 595-598 (1993).

[4] Hashimeto,V. and Shudo,K., Phytochemistry, 45, 551(1996).

[5] Vogel, A.I., "A Text Book of Practical Organic Chemistry" 3rd Ed., Longmann Group Limited, p.4-58 (1971).

[6] Upadhyay, M., in "Synthesis of some fixed ring heterocyclic compounds for studying their biological activity", A Ph.D. Thesis, Chemistry Department, Lucknow University, Lucknow, p.118(2005).